A novel activity of the Dickkopf-1 amino terminal domain promotes axial and heart development independently of canonical Wnt inhibition.

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Public Summary:

Scientific Abstract:
The secreted Dickkopf-1 (Dkk1) protein mediates numerous cell fate decisions and morphogenetic processes. Its carboxyl terminal cysteine-rich region (termed C1) binds LRP5/6 and inhibits canonical Wnt signaling. Paradoxically, the isolated C1 domain of Dkk1 as well as Wnt antagonists that act by sequestering Wnts, such as Frz-B, WIF-1 and Crescent, are poor mimics of the inductive and patterning activities of Dkk1 critical for heart and axial development. To understand the basis for the unique properties of Dkk1, we investigated the function of its amino terminal cysteine-rich region (N1). N1 does not bind LRP or Kremen nor inhibit Wnt signaling and has had no known function. We show that it can synergize with BMP antagonism to induce prechordal and axial mesoderm when expressed as an independent protein in Xenopus embryos. Moreover, we show that it can function in trans to complement the activity of C1 protein to mediate two embryologic functions of Dkk1: induction of chordal and prechordal mesoderm and specification of heart tissue from non-cardiogenic mesoderm. Remarkably, N1 also synergizes with WIF-1 and Crescent, indicating that N1 signals independently of C1 and its interactions with LRP. Since cleavage of Dkk1 is not detected, these results define N1 as a novel signaling domain within the intact protein that is responsible for the potent effects of Dkk1 on the induction and patterning of the body axis and heart. We conclude that this new activity is also likely to synergize with canonical Wnt inhibitory in the numerous developmental and disease processes that involve Dkk1.